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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,568	04/07/2005	Eric Adriaenssens	123439	8995

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OLIFF & BERRIDGE, PLC
P.O. BOX 320850
ALEXANDRIA, VA 22320-4850

EXAMINER	
HALVORSON, MARK	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
10/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,568	ADRIAENSSENS ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25,26,29 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25,26,29 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 23, 25, 26, 29 and 31-39 are pending and are under examination.

Objections to Claims withdrawn

The objection to claim 31 is withdrawn in view of Applicants amendment to claim 31.

- 35 USC § 112 1st paragraph rejection withdrawn

The rejection of claims 23 and 31 under 35 USC §112 for lack of enablement is withdrawn in view of Applicants amendment to claim 31 and Applicants arguments.

35 USC § 103(a) rejections withdrawn

The rejection of claims 25, 26 and 29 under 35 U.S.C. 103(a) as being unpatentable over Sakamoto et al, in view of WO 97/38313 and Varilek et al is withdrawn in view of Applicants amendments to claim 23..

35 USC § 103(a) rejections maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23, 31, new claims 32, 37-39 and claims 25 and 26 by amendment to claim 23, are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakamoto et al (cited previously) in view of Bigazzi et al (cited previously) and Pica et al (cited previously).

The claims are drawn to a method for the diagnosis of breast cancer comprising determining the presence in a biological sample obtained from a patient suspected of suffering from breast cancer of NGF that has been secreted by breast cancer tissue, wherein the biological sample is selected from the group consisting of blood, bone marrow, milk, cerebrospinal fluid and urine, wherein the presence of secreted NGF is demonstrated by the use of a ligand and an antiligand, wherein the ligand binds to the NGF.

Sakamoto et al disclose a method for diagnosing breast cancer by using immunohistochemisty on biopsy specimens to detect NGF (page 975, 2nd column, 3rd paragraph).

Sakamoto et al does not disclose determining the presence of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine or effusions, wherein the presence of secreted NGF is demonstrated by the use of a ligand and an antiligand, wherein the ligand binds to the NGF.

Bigazzi et al detected high levels of NGF in the serum of a patient with medullary carcinoma of the thyroid gland. (Table 1). Bigazzi et al use a competitive binding

radioimmunoassay to detect NGF in the serum using labeled NGF (ligand) and anti-NGF antibody (antiligand).

Pica et al detected high serum levels of patients with Kaposi's sarcoma. (Table 1).

One of ordinary skill in the art would have been motivated to apply Bigazzi et al and Pica et al's detection of NGF in the serum to Sakamoto et al's method for diagnosing breast cancer by using immunohistochemisty on biopsy specimens to detect NGF because of the simplicity of detecting a tumor antigen in serum as opposed to a tissue biopsy. It would have been prima facie obvious to combine Sakamoto et al's method for diagnosing breast cancer by using immunohistochemisty on biopsy specimens to detect NGF with Bigazzi et al and Pica et al's detection of NGF in the serum to simplify the assay for NGF in breast cancer.

Applicants argue that the applied references, alone or in combination, would not have rendered obvious the claimed invention because there would have been no reasonable expectation of success from combining and modifying the teachings of the applied references to produce the claimed invention. Applicants argue that none of the applied references, alone or in combination, teach or suggest that the NGF secreted by breast cancer tissue is present in blood, bone marrow, milk, cerebrospinal fluid and urine in levels sufficient to be a useful diagnostic tool for breast cancer. The Declaration submitted by Applicants on July 22, 2008 discloses that NGF was known to have a very short half-life (varying from less than one to five hours according to the experimental procedures. Applicants argue that the short half-life of NGF would have made it even more unpredictable for the presence of secreted NGF to be detected in blood, bone marrow, milk, cerebrospinal fluid and urine. Secreted NGF in the blood quickly binds to spinal nodes rich in TRKa receptors, thereby depleting the secreted NGF from the blood. Applicants argue that this also would have made it even more unpredictable for the presence of NGF to be detected in blood.

Applicants also argue that the change in the level of a protein secreted by cancerous tissue does not necessarily correlate with a similar change in the level of that protein in blood, bone marrow, milk, cerebrospinal fluid or urine. Applicants argue that

as described sections 1-111 of the attached Declaration, at the time of the claimed invention, it would not have been predictable that the change in the level of NGF in tissue would have correlated to a similar change in the level of secreted NGF present in blood, bone marrow, milk, cerebrospinal fluid and urine in levels sufficient to be a useful diagnostic tool for breast cancer. Accordingly, a change in the level of NGF in breast cancer tissue, as taught by Sakamoto, would not have automatically correlated to a similar change of the level of secreted NGF in such substances. It is noted that Applicants have only demonstrated an increase in NGF in the serum and has not demonstrated a corresponding increase in the level of NGF in bone marrow, milk, cerebrospinal fluid or urine.

Applicants also argue that the attached Declaration shows that an increased level of a protein secreted by colorectal cancer tissue does not correlate to an increased level of the secreted protein in blood, even though the protein is secreted by the cancerous tissue. The Declaration indicates that immunohistochemical analysis shows overexpression of the protein in tissues of cancer patients, as well as tissues of patients having benign lesions, as compared to tissues of healthy subjects. Levels of this secreted protein in the blood of both cancer patients and healthy subjects are equivalent. Applicants argue that this demonstrates that overexpression of a protein in cancer tissue does not necessarily lead to an increase in the secreted protein in the blood, even though the protein is secreted by the tissue. Applicants further argue that determining the presence in a biological sample of the protein secreted by the cancerous tissue could not have been expected to be useful for diagnosis of the cancer, wherein the biological sample comprises a substance selected from the group consisting of blood, bone marrow, milk, cerebrospinal fluid and urine. It is noted that the identity of the protein identified by Applicants to be overexpressed in colon cancer was not identified making it difficult to evaluate the relevance of Applicants findings to the present case.

Applicants Declaration submitted July 22, 2008 and arguments have been considered but are not persuasive. It was known in the art at the time the present invention was made that tumor antigens expressed on tumor tissues are commonly

found in serum, saliva, urine and other bodily fluids. Furthermore, it would be more likely for a secreted protein such as NGF to be found in bodily fluids. This is supported by the findings of Bigazzi et al and Pica et al that demonstrate the presence of NGF in serum. Applicants bring up several properties of NGF that make it less likely to be found in serum. However, the fact that NGF has been found in the serum in patients with cancer indicates that NGF can be found in the serum. Applicants have not disclosed sufficient reasons as to why one skilled in the art would not expect the secreted protein, NGF, to be found in the serum in patients with tumors overexpressing NGF, in light of the findings of Bigazzi et al and Pica et al. Applicants disclosure of protein 1 that is overexpressed in colorectal tumor tissue but not in serum has been considered but is not persuasive. First, the identity of protein 1 is not known and thus it is difficult to determine the relevance of Applicants finding. More importantly, NGF has been found to present in higher concentrations in specific cancers in Bigazzi et al and Pica et al. In addition, it is well known in the art that tumor antigens which are highly expressed in cancerous tissue are commonly found in the serum. Applicants have not supplied sufficient evidence to demonstrate that NGF would not likely be found in serum given the expression of NGF in breast cancer tissue. The findings of Bigazzi et al and Pica et al support the contention that it would have been predictable to detect NGF in higher concentrations in blood in breast cancer patients given the expression of NGF in breast cancer tissue. Applicants have not sufficiently explained why a person skilled in the art would not have a reasonable expectation of success to detect elevated levels of serum NGF in breast cancer patients given the elevated levels of NGF found in specific cancers in Bigazzi et al and Pica et al.

In addition, Applicants argue that there would have been no reason for one of ordinary skill in the art to combine Bigazzi et al and Pica et al with Sakamoto et al. Applicants argue that Bigazzi teaches that the level of an unidentified factor was increased in the serum of a single patient afflicted with a rare disease, a familial medullary thyroid carcinoma associated with a complex hereditary syndrome. Applicants argue that Bigazzi's teachings are directed to thyroid cancer, and Bigazzi is silent as to breast cancer and that Bigazzi merely speculates that the factor found in

the serum of the patient was NGF, but does not conclusively identify the factor as NGF. Applicants argue that Bigazzi was published in 1976, when no assay methods were available that would have positively identified the factor as NGF.

Applicants also argue that Pica is silent as to breast cancer altogether and that Pica does not teach or suggest that the KS tissue secretes NGF, and therefore fails to teach or suggest that the source of the NGF present in the serum is the KSR tissue.

Applicants arguments have been considered but are not persuasive. Bigazzi et al used an assay commonly used at the time to measure human NGF. Bigazzi et al used a competitive radioimmunoassay using labeled mouse NGF and antibodies to mouse NGF. Applicants have not supplied any evidence that demonstrates that the assay to measure human NGF using the method in Bigazzi et al did not in fact measure human NGF. The fact that Bigazzi et al does not refer to breast cancer is not directly relevant. Bigazzi et al demonstrate that human NGF can be detected in blood. At the time of the invention it was common in the art to use serum to detect tumor antigens because the procedure to detect tumor antigens in serum is less invasive than the procedure to detect tumor antigens in tissue. Likewise Pica et al demonstrates that human NGF can be detected in blood. Both Bigazzi et al and Pica et al involved tumors.

NEW REJECTION: Based on amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakamoto et al (cited previously, in view of Bigazzi et al (cited previously) and Pica et al (cited previously) and further in view of Varilek et al (cited previously).

The claims are drawn to a method for the diagnosis of breast cancer comprising determining the presence in a biological sample obtained from a patient suspected of suffering from breast cancer of NGF that has been secreted by breast cancer tissue, wherein the biological sample is selected from the group consisting of blood, bone marrow, milk, cerebrospinal fluid and urine, wherein the detection of NGF is demonstrated by culturing NGF-sensitive cell in the presence of the biological sample.

Sakamoto et al, Bigazzi et al and Pica et al have been described supra.

Neither Sakamoto et al, Bigazzi et al nor Pica et al teach the detection of NGF by culturing NGF-sensitive cell in the presence of the biological sample.

Varilek et al describe the detection of secreted NGF by culturing a biological sample in the presence of the NGF-sensitive cell, PC-12. (page G446, 2nd paragraph).

One of ordinary skill in the art would have been motivated to apply Varilek et al's method of detecting NGF from cell supernatants to Sakamoto et al, Bigazzi et al and Pica et al's method of method of detecting NGF from bodily fluids because of the sensitivity of detecting NGF from cell supernatants. (Varilek et al, Abstract). It would have been prima facie obvious to one skilled in the art to have combined Sakamoto et al, Bigazzi et al and Pica et al's method of detecting NGF with Varilek et al method of detecting NGF to detect NGF using another procedure which may be more sensitive than the immunoassay.

Applicants argue that Varilek fails to teach or suggest that secreted NGF is found in the blood, bone marrow, milk, cerebrospinal fluid or urine of the humans with colon adenocarcinoma and/or the fetal rats with nonmalignant enterocyte. Applicants also argue that Varilek also fails to teach or suggest that the presence of NGF in the tissues of human patients with colon adenocarcinoma or fetal rats with nonmalignant enterocyte correlates to the presence of secreted NGF in the blood, bone marrow, milk, cerebrospinal fluid or urine of the human patients and fetal rats. Moreover, Varilek et al is silent as to breast cancer altogether.

Applicants arguments have been considered but are not persuasive. In response to applicant's arguments against Varilek et al, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Varilek et al is being used in the current rejection to demonstrate that another assay for NGF may be used instead of the immunoassays described in Bigazzi et al and Pica et al.

Claims 23 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakamoto et al (cited previously, in view of Bigazzi et al (cited previously) and Pica et al (cited previously) and further in view of Billing-Medel et al (US Patent Application Publication 2003/0104364 published June 5, 2003, filed June 25, 1998).

The claims are drawn to a method for the diagnosis of breast cancer comprising determining the presence in a biological sample obtained from a patient suspected of suffering from breast cancer of NGF that has been secreted by breast cancer tissue, wherein the biological sample is blood, bone marrow, milk, cerebrospinal fluid and urine,

Sakamoto et al, Bigazzi et al and Pica et al have been described supra.

Neither Sakamoto et al, Bigazzi et al nor Pica et al teach NGF in urine, milk, bone marrow, or cerebrospinal fluid.

Billing-Medel et al discloses the detection of breast tumor markers in urine, milk, bone marrow and cerebrospinal fluid. (paragraphs 6 and 65).

One of ordinary skill in the art would have been motivated to apply Billing-Medel et al's method of detecting breast cancer tumor antigens from urine, milk, bone marrow and cerebrospinal fluid to Sakamoto et al, Bigazzi et al and Pica et al's method of detecting NGF from bodily fluids because Billing-Medel et al disclose other types of bodily fluid that may be used to detect breast cancer tumor antigens. It would have been prima facie obvious to one skilled in the art to have combined Sakamoto et al, Bigazzi et al and Pica et al's method of detecting NGF with Billing-Medel et al's method of detecting breast cancer tumor antigens from urine, milk, bone marrow and cerebrospinal fluid to have a more complete tumor antigen detection system.

Summary

Claims 23, 25, 26, 29 and 31-39 stand rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571)

272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson
Patent Examiner
571-272-6539

/MISOOK YU/
Primary Examiner, Art Unit 1642